REMARKS

Claims 58-103 are currently pending in this application. Claims 58-103 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. Claims 60-103 are rejected for obviousness-type double patenting over claims 1-25 of U.S. Patent No. 6,251,590 in view of Chee et al. (U.S. Patent No. 5,837,832). By this reply, Applicants cancel claims 59-62, 64, 73-79, 81-87, 89-90, and 95-96, amend claims 58, 63, 65-66, 68-72, 80, 88, 91-94, 97-99, and 101-103, provide new claims 104-106, and address each of the rejections below.

Support for the Amendments

Support for the amendment to claim 58 is found in prior claim 58 and in the specification on, e.g., page 4, lines 10-17, page 22, lines 21-24, page 25, lines 1-15, and page 57, line 14, through page 58, line 12. Support for the amendment to claims 63 and 99 is found in the specification on, e.g., page 23, line 24, through page 24, line 2. Support for the amendment to claim 65 is found in the specification on, e.g., page 25, lines 1-15. Support for the amendment to claim 66 is found in the specification on, e.g., page 8, line 30, through page 9, line 8. Support for the amendment to claim 68, and for new claim 104, is found in the specification on page 22, lines 21-24. Support for the amendment to claims 69-72, 80, 88, and 93 is found in prior claims 69-72, 80, 88, and 93. Support for the amendment to claims 91, 92, and 94 is found in the specification on, e.g., page 22, lines 21-24, and page 25, lines 1-15. Support for the amendment to claim 97 is found in prior claim 98. Support for the amendment to claim 98 is found in prior claim 97. Support for the amendment to claims 101-103 is found in prior claims 101-103, and in the specification on, e.g., page 22, lines 21-24. Support for the amendment to new claims 105 and 106 is found in the specification on, e.g., page 58, line 16, through page 61, line 2. No new matter is added by the amendment.

Obviousness-Type Double-Patenting Rejection

Claims 60-103 are rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 6,251,590 in view of Chee et al. (U.S. Patent No. 5,837,832). In response to the double patenting rejection, Applicants submit a terminal disclaimer herewith, which waives the terminal portion of the term of the entire patent to be granted upon the above-identified application subsequent to the expiration date of U.S. Patent No. 6,251,590. In view of the terminal disclaimer, the rejection of claims 60-103 can be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 58-103 are rejected under 35 U.S.C. § 112, first paragraph, for lack of an adequate written description. The Examiner reasons that the subject matter of claims 58-103 was "not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention" (Office Action, p. 3). The Examiner's argument is that the sequences of an insufficient number of exemplary oligonucleotides have been provided in the specification. Applicants respectfully disagree, but have amended claims 58, 63, 65-66, 68-72, 80, 88, 91-94, 97-99, and 101-103, and have provided new claims 104-106, to more clearly describe the presently claimed invention. Furthermore, as is discussed below, Applicants believe that the Examiner has misapplied the written description rejection in the present case.

Applicants' Invention

Applicants' invention, as is recited in present claims 58, 63, 65-66, 68-72, 80, 88, 91-94, and 97-106, is directed to a device and a method for making the device. The device comprises a support material (e.g., a filter, a membrane, or a chip) and single-stranded oligonucleotides (e.g., DNA or RNA molecules) of between 5 and 100 nucleotides in length that are attached to the support material in a serial arrangement. The support material contains at least two different oligonucleotides: one that contains a sequence that is complementary to and specific for an exon or an intron of a gene, and one that contains a sequence that is complementary to and specific for an exon-exon or exon-intron junction region of a gene.

The present invention was conceived when Applicants determined that the nucleic acid sequence differences between a "wild-type" gene product and an "differentially spliced" gene product, e.g., the inclusion or exclusion of an exon, an intron, or an exon-exon/exon-intron junction region, as occurs upon differential RNA processing, can be used as probes to obtain functional information from a sample (i.e., a cell), such as the presence or absence of disease, the efficacy of novel therapeutic products on a cell, tissue or organism, and to obtain a toxicological profile or potency profile of a compound when administered to a cell, tissue, or organism. Applicants' invention has, in effect, improved upon and simplified a known technique, that of northern blot analysis, in which mRNA from a test sample is immobilized on a support membrane (i.e., nitrocellulose) and probed with an oligonucleotide molecule that is the complement of a single, specific nucleic acid sequence known or thought to be present in a mRNA present in the test sample. The prior art technique is limited, though, in its use of only one probe at a time, which only allows the determination of the presence or absence of a single sequence in the test sample. Applicants' invention, on the other hand, allows the identification of the presence or absence of one or more differential splicing events in a test sample. Therefore, Applicants' invention yields a much higher amount of data with fewer preparations and further allows for a more complex analysis of the test sample.

Another advantage of Applicants' invention is that the functionality of the device can be

modified depending on the selection of oligonucleotides used in the manufacture of the device. In this regard, the oligonucleotides are a variable component of Applicants' device and can be user-defined to correspond to the particular needs of the artisan. Therefore, it is left up to the artisan to determine how the device will be used and what oligonucleotides should be selected to achieve that end.

Yet another advantage of Applicants' invention is that, to practice the invention, one simply has to obtain or generate the oligonucleotides to be used (i.e., the complement to an exon, an intron, or a junction region of a differentially spliced gene). Because differentially spliced genes are known in the art, as is discussed below, one skilled in the art can select specific oligonucleotides based on knowledge in the art of sequences that correspond to differentially spliced exons, introns, or junction regions of a gene, such that the selection will yield a device that will address the specific needs of the artisan. Alternatively, the artisan can follow the methods described in Applicants' specification, as is discussed below, to obtain such oligonucleotides (see, e.g., p. 14, line 5, through p. 19, line 11, page 24, lines 3-32, and pages 42-53). It is important to note that what is required to practice Applicants' invention (and correspondingly, what the inventors need to have had conceptually at the time of filing) is the understanding that the oligonucleotides that are complementary to and specific for differentially spliced exons, introns, or junction regions of a gene can be used to generate the aforementioned functional information; having *a priori* knowledge of the actual nucleic acid sequence of the oligonucleotides is not necessary. There is no dispute that Applicants have sufficient information in the specification as to this point. For this reason, Applicants argue that the Examiner's rejection of claims 58-103 under 35 U.S.C. § 112, first paragraph, for lack of written description has been misapplied

The Written Description Requirement: The Legal Standard

The written description requirement, as set forth in 35 U.S.C. § 112, first paragraph, requires that the "specification shall contain a written description of the invention." The M.P.E.P. § 2163 states:

> The written description requirement has several policy objectives. "[T]he 'essential goal' of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." *In re Barker*, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). Another objective is to put the public in possession of what the applicant claims as the invention. See *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998).

Furthermore, "[t]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention" (M.P.E.P. § 2163).

> An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including *description of an actual reduction to practice*, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). (M.P.E.P. § 2163; emphasis added.)

Historically, the issue of whether claims pending in an application satisfy the written description requirement was raised in cases where the subject matter at issue, which was to be recited in the claims, was believed to represent "new matter" that was not adequately supported in the original specification or available from the prior art. More recently, though, written description rejections arise in cases where the claimed invention as a whole is not adequately described, for example, "where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function" (M.P.E.P. § 2163). The prime example of such a situation, described in the M.P.E.P., is an application supporting a claim to a biomolecule sequence, e.g., a nucleic acid or polypeptide sequence. The M.P.E.P. § 2163

states that a biomolecule sequence which is "described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

In order to fulfill the written description requirement of § 112, the patent specification does not need to describe exactly all the subject matter of specific embodiments of a component part recited by claims if such embodiments are present in the prior art. *In re Daniels*, 114 F.3d 1452, 46 U.S.P.Q.2d 1788 (Fed. Cir. 1998); *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 227 U.S.P.Q. 117 (Fed. Cir. 1985). Rather, the specification must clearly allow a person of ordinary skill in the art to recognize that the inventor has invented what is claimed. *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 45 U.S.P.Q.2d 1498 (Fed. Cir. 1998). In applying this standard, the Federal Circuit has held that the specification must convey with reasonable clarity to a skilled artisan that the inventor "was in possession of the invention" at the time of filing. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991).

Applicants have Satisfied the Written Description Requirement

Applicants' invention is a device that employs oligonucleotides that are complementary to and specific for differentially spliced exons, introns, and junctions regions of one or more genes; a component of the device that provides output regarding the functional state of a sample. The device allows one of ordinary skill to identify the presence or absence of at least one differentially spliced gene product in a test sample containing at least one nucleic acid molecule. Applicants' invention is <u>not</u> the discovery of oligonucleotides per se, rather, it is the *combination* of a support material and oligonucleotides that are complementary to and specific for differentially spliced exons, introns, and junctions regions of one or more genes arranged thereon for a particular purpose. For the purposes of written description, all that is required is that Applicants' specification describe the claimed invention in sufficient detail such that one skilled in the art can <u>reasonably</u> conclude that the inventor had possession of the claimed invention (M.P.E.P. § 2163; *Regents of the University of California v. Eli Lilly & Co., supra*). Applicants can demonstrate possession by providing an actual reduction to practice of the

claimed invention (see, e.g., *Pfaff v. Wells Elecs., Inc., supra*; *Regents of the University of California v. Eli Lilly & Co., supra*; and *Amgen, Inc. v. Chugai Pharmaceutical, supra*), or by describing the invention with all of its limitations using a description that clearly conveys the claimed invention (*Lockwood v. American Airlines, Inc., supra*). "The description need only describe in detail that which is new or not conventional." (*Hybritech v. Monoclonal Antibodies*, 802 F.2d 1367, at 1384, 231 USPQ 81, at 94 (Fed. Cir. 1986)). Applicants have clearly satisfied all of these requirements.

Applicants Specification Describes an Actual Reduction to Practice

Applicants clearly demonstrate possession of the claimed device by presentation of several examples of a reduction to practice of the invention.

On page 53, line 4, through page 54, line 23, of the specification, Applicants describe the preparation of two distinct differential splicing libraries. One library is derived from untreated HepG2 cells and is composed of nucleic acid molecules that are complementary to and specific for "normally" spliced RNA products. The second library is derived from HepG2 cells exposed to a toxic agent, in this case ethanol, which is known to cause cytotoxicity and DNA degradation via internucleosomal fragmentation. The second library is composed of nucleic acid molecules that are complementary to and specific for "abnormal, differentially spliced" RNA products that result from the ethanol treatment of the cells. Applicants further describe the preparation of two identical filters containing nucleic acid molecules derived from the first library (untreated, NT) and two identical filters containing nucleic acid molecules derived from the second library (ethanol-treated, Tr; i.e., a device as is recited in present claims 58 and 91-93, and claims dependent therefrom). mRNA molecules obtained from untreated HepG2 (the test sample) is applied to one of the two filters containing nucleic acid molecules from the NT library and to one of the two filters containing nucleic acid molecules from the Tr library. Conversely, mRNA molecules obtained from ethanol-treated HepG2 cells is applied to the second filter containing nucleic acid molecules from the NT library and to the second filter containing nucleic acid molecules from the Tr library. The differential hybridization profile that results is shown in Figure 12 of the specification, which shows that the nucleic acid molecules from the NT library

(NT clones), which are derived from untreated cells (NT) and which correspond to qualitative differences specific to the untreated condition, preferentially hybridize with cDNAs from untreated cells (compare Bands NT to Bands Tr under NT clones). Alternatively, the nucleic acid molecules from the Tr library (Tr clones), which are derived from ethanol-treated cells (Tr) and which correspond to qualitative differences specific to the treated condition, preferentially hybridize with cDNAs from ethanol-treated cells (compare Bands Tr to Bands NT under Tr clones). In this example, Applicants were clearly able to demonstrate qualitative differences between a treated and an untreated condition using nucleic acid molecules that are complementary to and specific for differentially spliced exons, introns, or junction regions specific to the treated or untreated condition. Applicants note that the device described in this example utilized nucleic acid molecules having an unknown sequence. Therefore, practicing the invention, as illustrated by this example, did not require *a priori* knowledge of the nucleic acid sequence of any of the nucleic acid molecules attached to the support membrane.

In addition, as is discussed above, the inventive device can be prepared using one or more oligonucleotide probes corresponding to a specific differentially spliced domain of a known gene. On page 58, line 16, through page 61, line 2, the specification describes three differentially spliced genes, MACH-α, BCL-X, and FAS receptor, which are known to be differentially spliced in a cell exposed to a compound (in this case camptothecin or ethanol). The specification states that "Camptothecin induces a decrease in the expression of isoform MACH-α1 and an increase in isoform MACH-α3[,]...induces the appearance of a new bcl-X isoform...[, and] induces a decrease in the wild type form of the fas receptor, replaced by expression of a shorter isoform which may correspond to FasΔ TM" (Specification, p. 60, lines 21-26). When treated with ethanol, the cells exhibit a decrease in the expression of bcl-X, an increase in the expression of a shorter bcl-X isoform, and "an increase in the expression of a long wild type form of the fas receptor at the expense of the shorter isoform" (Specification, p. 60, lines 27-30). This example clearly demonstrates that the skilled artisan can utilize oligonucleotides corresponding to the complement of art-recognized differentially spliced exons, introns, or junction regions of known genes, especially in cases where the gene is known to be differentially spliced in response to a physiological condition of a cell (i.e., exposure to a compound).

In example 1.4, which relates to the production of profiled libraries representative of human endothelial cells, the specification describes the identification of a particular variant of the SH2 domain of the SHC protein, designated ΔSHC, using the methods of the invention (see p. 47, line 10, through page 51, line 8, of the specification). This variant is generated due to differential splicing of the SHC protein that results in a deletion corresponding to bases 1198-1293 of the SH2 domain (SEQ ID NO: 8) and is observed in ECV cells undergoing apoptosis. The specification states that oligonucleotides corresponding to the complement of the ΔSHC sequence (e.g., SEQ ID NO: 10, which corresponds to the junction region resulting from the alternative splicing of SHC around nucleotide 1198, see p. 50, lines 2-3) can be used to identify the expression of ΔSHC and/or any variant of SHC in a biological sample.

These examples clearly demonstrate that Applicants had reduced two very different embodiments of the invention (using an unknown and a known sequence) to practice as of the filing date of the present application, and therefore demonstrates unequivocally that Applicants were in possession of the claimed invention. For this reason, present claims 58, 63, 65-66, 68-72, 80, 88, 91-94, and 97-106 satisfy the written description requirements of 35 U.S.C. § 112, first paragraph.

Applicants have Described the Claimed Device with All of its Limitations

Possession of a claimed invention can also be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention (*Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997)). The written description standard does not require a detailed description of those features of an invention that were well known to or understood by the skilled artisan at the time of filing, but rather, "[t]he description need only describe in detail that which is new or not conventional" (*Hybritech v. Monoclonal Antibodies, supra*; emphasis added). Therefore, to satisfy the written description requirement, Applicants need only describe in detail those features that were not new or were unconventional in the art at the time of filing.

As is discussed above, the presently claimed invention is a device that is the combination

of a solid support membrane and oligonucleotides that are complementary to and specific for exons, introns, and junction regions of a differentially spliced gene. To satisfy the written description requirement, what must be described in detail is the claimed device, which was not new or conventional in the art at the time of filing. Applicants have clearly satisfied this requirement, as is clear from the description above of Applicants' reduction to practice of the presently claimed device. In contrast, the oligonucleotides, which are the variable, user-defined component of the present device, need not be described in more detail than that which is provided in the specification because this portion of the device was not new or unconventional in the art at the time of filing. Splicing of genes was well appreciated prior to Applicants' invention. Exons, introns, and junction regions of many genes, the presence or absence of which varies due to differential RNA processing, were well-known to the skilled artisan prior to Applicants' filing date. Therefore, the genus of oligonucleotides that make up one part of the inventive device was not new or unconventional at the time the application was filed, and the skilled artisan would not require a detailed description in the specification to be apprised of this component of the inventive device.

In the previous Reply to Office Action, filed on September 5, 2003, Applicants asserted that evidence of this could be found by performing a search using, e.g., PubMed (www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed) and the keywords "alternative splicing," "differential splicing," and "trans-splicing," and limiting the search to articles published prior to March 24, 1998, the earliest priority date for the present application. Applicants argued that such a search yields a search result of 6,519 references. Many of these references identify not only the presence of differentially-spliced gene products (i.e., the "normal transcript" and the "differentially-spliced transcript(s)"), but also the specific region of variability between the various transcripts and the conditions under which the differential splicing occurs. Therefore, exons, introns, and junction regions of differentially-spliced genes, and the nucleic acid molecules corresponding to these regions, were known in the art. The Examiner states that "as no references of the 6,519 set [has] been provided, the evidence of a number of references that have the keyword is not found convincing. It is unclear as to what the references teach or do not teach" (Office Action, p. 4). To satisfy the Examiner's concern with respect to what is disclosed

by the references identified by the search, Applicants provide herewith as Exhibit A a copy of 100 representative abstracts of references identified by the search. A review of the abstracts confirms that differentially spliced genes across many genera were known to the skilled artisan prior to Applicants' filing date. Therefore, the genus of oligonucleotides recited in present claims 58, 63, 65-72, 80, 88, and 91-94, and 97-107 would have been known to the skilled artisan at the time of filing the present application and would not have been new or unconventional in the art. To satisfy the written description requirements of 35 U.S.C. § 112, first paragraph, by the standard set forth in *Hybritech v. Monoclonal Antibodies* (*supra*), Applicants' specification would not need to describe the specific sequence of oligonucleotides complementary to and specific for variable exons, introns, and junction regions of a differentially spliced gene in any more detail than is already provided by Applicants' specification. Thus, Applicants need not describe the oligonucleotides to the level required by the Examiner (see Office Action, p. 4-5).

Furthermore, the specification clearly describes the genus of oligonucleotides by using art-known terms and by providing several examples of differentially spliced genes. After reading Applicants' specification, which provides a thorough written description of the genus of oligonucleotides to be employed, the skilled artisan can easily envisage the genus of oligonucleotides for attachment to the support material to yield the device of present claims 58 and 91-93, and claims dependent therefrom, or to make the device using the method of present claims 94 and 97-107 for a great variety of purposes. Moreover, several databases of differentially-spliced genes, including specific exons, introns, and junction regions are available to the skilled artisan, who can use these databases to provide the oligonucleotides for use in the presently claimed device (see, e.g., http://hazelton.lbl.gov/~teplitski/alt/; http://www.ebi.ac.uk/asd/; and http://www.bioinformatics.ucla.edu/~splice/HASDB/). The skilled artisan can also follow Applicants' methods for obtaining oligonucleotides, which is also thoroughly described in the specification (see, e.g., p. 14, line 5, through p. 19, line 11, page 24, lines 3-32, and pages 42-53). Therefore, the skilled artisan, by following the teachings contained in the present application, would have a clear understanding, based on the written description in Applicants' specification, of the genus of oligonucleotides for use in the present device and could

obtain those oligonucleotides using one of several methods provided in the specification.

As is evident from the above discussion, Applicants have clearly demonstrated possession of the claimed device by describing the device with all of its limitations, as is required (see M.P.E.P. § 2163, *supra*). Because Applicants need not describe those aspects of the invention that were not new or unconventional in the art at the time of filing (*Hybritech v. Monoclonal Antibodies* (*supra*), the genus of oligonucleotides recited in the present claims, which were well known to and appreciated by the skilled artisan prior to Applicants' filing date, need not be described in any more detail than that already provided in the specification. For this reason as well, Applicants respectfully request that the rejection of claims 58-103 under 35 U.S.C. § 112, first paragraph, for lack of written description be withdrawn.

In the event that the Examiner disagrees, though, Applicants submit that the skilled artisan would have clearly understood what was encompassed by the genus of recited oligonucleotides, based on Applicants thorough written description in the specification of several exemplary oligonucleotides, which are representative of the genus of oligonucleotides as a whole. One representative example is exon 2 of the p130 protein of the retinoblastoma family, which the specification teaches is differentially spliced in the cells of patients with small cell lung carcinoma (see the specification at p. 29, lines 10-13). A second representative example is the junction region comprising the mutated donor splice site of the p16INK4a gene, which the specification states is mutated in the cells of patients with certain non-small cell lung carcinomas (see the specification at p. 29, lines 15-19). The specification also describes differentially-spliced variants of the Wilt's tumor suppressor gene (WT1), the neurofibrin NF1 gene, the HDM2 gene, the p53 gene, the MACH-α (Caspase-8) gene, the BCL-X gene, and the FAS receptor gene (see the specification at, e.g., p. 29, lines 19-32, and p. 58, line 16, through p. 61, line 2). These examples are provided to exemplify and not limit the present invention of claims 58, 63, 65-72, 80, 88, 91-94, and 97-107.

As is stated above, though, to practice the present invention, it is not required that the nucleic acid sequence of the oligonucleotides be known *a priori*. The specification also teaches that nucleic acid molecules present in a cDNA library representative of a given physiological

state of a biological sample (e.g., a disease state, such as cancer) can be used as a source of the oligonucleotides for use in the presently claimed device. The specification teaches that libraries made by the provided method, which consist of cDNA inserted into plasmid or phage vectors, can be deposited on support materials to produce the presently claimed devices (see, e.g., page 19, line 13, through page 23, line 23). These libraries can be readily produced or obtained by one skilled in the art and, following the teachings contained in the present specification, the nucleic acid molecules derived therefrom can be used in the presently claimed devices.

Therefore, based on the above information, particularly when taken together, it should be clear to the Examiner and one skilled in the field of the invention that Applicants were in possession of the inventive device based on the detailed description of the invention in the specification. Again, Applicants submit that the written description requirements of 35 U.S.C. § 112, first paragraph have been satisfied.

Summary

Applicants' specification clearly satisfies the written description requirement of 35 U.S.C. § 112, first paragraph, by providing a thorough description of the claimed invention with all of its limitations such that one skilled in the art can reasonably conclude that Applicants were in possession of the claimed device (M.P.E.P. § 2163; *Regents of the University of California v. Eli Lilly & Co.*, *supra*; *Lockwood v. American Airlines, Inc.*, *supra*). Applicants met this standard by demonstrating an actual reduction to practice (see, e.g., *Pfaff v. Wells Elecs., Inc.*, *supra*; *Regents of the University of California v. Eli Lilly & Co.*, *supra*; *Amgen, Inc. v. Chugai Pharmaceutical*, *supra*), and by describing the claimed device with all of its limitations (see, e.g., *Lockwood v. American Airlines, Inc.*, *supra*; *Regents of the University of California v. Eli Lilly & Co.*, *supra*). As evidence of possession of the device with all of its limitations, Applicants have also provided a considerable description of exemplary oligonucleotides, far in excess of that required by the written description requirement, which only requires a description of that which is new or unconventional. The standard applied by the Examiner, and which serves as the basis for the present rejection, would require Applicants to describe the genus of oligonucleotides, which was well known prior to Applicants' filing date, in more detail that that which has been required by

the Federal Circuit (*Hybritech v. Monoclonal Antibodies, Inc., supra*). Therefore, the Examiner's basis for the present rejection is improper and the rejection of claims 58-103 should be withdrawn.

While the above comments describe the knowledge and skill of one in the relevant art at the time the application was filed with respect to differential splicing events and the recognition and identification of differentially-spliced exon, intron, and junction regions of genes, Applicants reiterate that the instant invention alone discloses a novel concept of functional genomics and genetic analysis that utilizes this knowledge of differential splicing events and provides novel products for performing such analyses. No prior art of record describes the use of oligonucleotides that are complementary to and specific for exons, introns, and junction regions of genes in methods for monitoring differential splicing events, for the manufacture of devices for monitoring the occurrence of differential alternative exons and introns splicings in a sample, or the advantage of monitoring, in a sample, genetic variability due to differential splicing events, as is presently disclosed and claimed. Therefore, for all of the reasons provided above, Applicants submit that present claims 58, 60-61, 63, 65-6, 68-72, 80, 88, 91-94, and 97-106 satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, and that the Examiner has misapplied the requirement in his rejection of claims 58-103. Accordingly, Applicants respectfully request that the rejection of claims 58-103 under 35 U.S.C. § 112, first paragraph, for lack of written description, be withdrawn.

CONCLUSION

In light of the foregoing amendment and remarks, Applicants submit that the claims are novel and inventive over the prior art and respectfully request favorable reconsideration of the present application. In particular, it is believed that the claims are now in condition for allowance, and a notification to that effect is earnestly solicited.

An interview with the Examiner and the Examiner's Supervisor is requested in the event the present Amendment is not believed to place the application in condition for allowance.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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